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A BRIEF REVIEW ON SUSTAINED RELEASE AND TASTE MASKED SUSPENSION

ABSTRACT

Taste is an important factor in the development of dosage form. The problem of bitter and obnoxious taste of the drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. In order to ensure patient compliance bitterness masking becomes essential. The purpose of this work was to mask the intensively bitter taste of drug using ion exchange resin and to formulate oral suspension of the taste mask drug. When suspension is swallowed bitter tasted may not be felt because ion exchange resin complex does not release drug at salivary pH. When it comes in contact with acidic environment of stomach, the complex will be broken down releasing the drug which may then observed. Bath method was used for formation of drug resin complex. Various ion exchange resins such as Ionex QM 1011 and Indione 244 were tried to unpainted taste masked drug resin complex. The present study aims to provide an overview about the Sustained release and taste masked suspensions using ion exchange resins their methods of preparation and their evaluation in brief.

KEYWORDS: Obnoxious taste, Ion exchange resins, taste masked.

INTRODUCTION

Tablets and capsules are unsuitable for administering high doses of Active Pharmaceutical Ingredient (API) since individual large dose is difficult to swallow, or require the administration of several tablets or capsules at a time, making it less patient compliant. Also chewable tablets are also not ideal with pediatric and geriatric patients due to need of chewing, poor taste masking and lack of control release possibility. Oral liquid suspensions are majorly designed for the patients with difficulty in swallowing. But their controlled release form is also tricky due to the chances of premature release of the API in the suspending media during storage. This produces a significant challenge and accounts for the fact that there are few sustained release oral suspension formulations. Different methods are mentioned hereafter for overcoming the problem.

SUSPENSION

Pharmaceutical suspensions are uniform dispersions of solid drug particles in a vehicle in which the drug has minimum solubility. Particle size of the drugs may vary from one formulation to the other depending on the physicochemical characteristics of the drug and the rheological properties of the formulation.

Reasons for suspension:

a) Drugs chemically unstable in solution are usually stable in suspended form. b) Convenient dosage form for large doses. c) Safe and compliant for infants and Children. d) For insoluble or poorly soluble API.

Criteria to be met by drug proposed to be formulated in sustained release

Dosage forms

a) Desirable half-life

The half life of a drug is an index of its residence time in the body. If the drug has a short half life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from, and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

b) High therapeutic index

Drugs with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities eg. Digitoxin.

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c) Small dose of the drug product

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undetermined. This is chiefly because the size of a unit dose controlled release formulation would become too big, to administer without difficulty.

d) Desirable absorption and solubility characteristics

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulations is therefore unrealistic and may reduce overall absorption efficiency.

e) Desirable absorption window

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the absorption window'. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable.

f) First pass clearance

Delivery of the drug to the body in desired concentrations is hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release forms.

ION EXCHANGE RESINS

Ion exchange resins are water insoluble cross-linked polymers containing a salt-forming group at repeating positions on the polymer chain and have the ability to exchange counter-ions within aqueous solutions surrounding them.
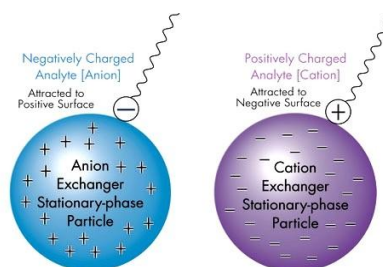
Ion exchange resins have been increasingly used as taste masking agents.

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Desired properties of pharmaceutical grade Ion Exchange Resins are:

a) Fine, free flowing powders

b) Particle size of 25 - 150 microns

c) Contain functional group that capable of exchanging ions and/or ionic groups

d) Insoluble in all solvents & all pH conditions.

e) Not absorbed by body

Taste masking and its advantages

Taste masking- apparent reduction in the unpleasant taste by using a suitable agent.

Taste masking technology includes two aspects:

- Selection of suitable taste masking substance such as polymers, sweeteners, flavors, amino acids etc.
- Selection of suitable taste masking techniques.

A suitable taste masking technique can powerfully impact both, quality of taste masking and   process effectiveness.

There are many techniques developed for taste masking of bitter drugs. They are as follows-

- Addition of flavoring and sweetening agents.
- Complexation with ion- exchange   ·
- Micro encapsulation.
- Prodrug approach
- Inclusion complexation
- Granulation
- Multiple emulsion technique
- Gel formation
- Bitterness inhibitors
- Miscellaneous

Advantages of Taste Masking

Some of the advantages of taste masked tablets include

a) Taste masking of bitter drugs improve patient's compliance.

 b) It also improves the stability of some drugs

c) It also improves the therapeutic efficacy.

d) It also improves the bioavailability of certain drugs.

e) It also improves the organoleptic characteristics of drugs.

Ion Exchange Resins as an Approach towards Taste

- One of the popular approaches in the taste masking of bitter drugs is based on IER.
- IER are solid and suitably insoluble high molecular weight poly electrolytes that can exchange their   mobile ions of equal charge with the surrounding medium.
- For taste masking purpose weak cation exchange or weak anion exchange resins are used, depending on the nature of drug.
- The nature of the drug resin complex formed is such that the average Ph of 6.7 and cation concentration of about 40 meq / L in the saliva are not able to break the drug resin complex but it is weak enough to break down by hydrochloric acid present in the stomach.
- The drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected.

Advantages of Resins as Taste Masking Agents

- Resins being poly electrolytes have extensive binding sites leading to very high drug loading ability.
- They are chemically inert and free from local and systemic side effects.
- All conventional solid, semisolid and liquid dosage forms can be prepared by using resins.
- They have been used in selective separation of pharmaceuticals from mixtures
- Being stable to all sterilization means, can be formulated into all sterile dosage forms.

Role of Ion Exchange Resins In Sustained Drug Delivery Systems

The usage of IER during the development of sustained release formulations plays a significant role because of their drug retarding properties and prevention of dose dumping. The drug resinates can also be used as drug reservoirs, which causes a change in drug release characteristics. The slowness of uptake and release of medicament from ion exchange resin has proved to be effective in solving the problem of dose dumping by conventional dosage forms.

Drug can be bound to the ion exchange resin by either repeated exposure of the resin to the drug in a chromatographic column (column method) or by prolonged contact of resin with the drug solution (batch method). Drugs are attached to the oppositively charged resin substrates or resinates through weak ionic bonding so that dissociation of the drug-resin complex does not occur under salivary pH conditions. This suitably masks the unpleasant taste and odour of drugs.

Thus the aim of present research work was to formulate & evaluate oral taste masked suspension of antitussive drug.

MICROENCAPSULATION

Microencapsulation is a rapidly expanding technology. As a process, it is a means of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersion. Microencapsulation provides the means of converting liquids to solids, altering colloidal and surface properties, providing environmental protection and of controlling the release characteristics or availability of coated materials.

Application of microencapsulation might well include sustained release for prolonged action medication, taste masking, powders, suspensions, single layered tablets containing chemically incompatible ingredients and new formulation concepts for creams, ointments, aerosols, dressings, plasters, suppositories and Injectable.

Reasons for Microencapsulation

- The primary reason for microencapsulation is found to be either for sustained or prolonged drug release.(Lachman L, et al., 1990)

- This technique has been widely used for masking taste and odor of many drugs to improve patient compliance.(Elwood P.C., et al., 1997)

- This technique can be used for converting liquid drugs in a free flowing powder.(Dayton, et al.,1966)

- The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by   microencapsulation.(Lachman L, et al., 1990)

- Incompatibility among the drugs can be prevented by microencapsulation.(Lachman L, et al., 1990)

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- Vaporization of many volatile drugs e.g. methyl salicylate and peppermint oil can be prevented by microencapsulation.(Lachman L, et al., 1990)

- Many drugs have been microencapsulated to reduce toxicity and GI irritation including ferrous sulphate and KCl.(Elwood P.C.,et al.,1997) (Arnold J.,et al.,1980)

- Alteration in site of absorption can also be achieved by microencapsulation.(Sudetcum R.H.,et al., 1981)(Tice T.R.,et al.,1981)

- Toxic chemicals such as insecticides may be microencapsulated to reduce the possibility of sensitization of factorial person.

Methods Employed In Microencapsulation

Many methods have been developed to prepare microparticles since particles have found useful application in various fields. Various conventional methods for preparation of microcapsules are as follows:

- Pan coating

- Spray drying and spray congealing

- Multiorifice centrifugal process

- Polymerization

- Air suspension technique

- Coacervation phase separation

- Melt dispersion technique

- Solvent evaporation.

Solvent evaporation technique:

The solvent evaporation process is carried out in a liquid manufacturing vehicle. The microcapsules coating material is dissolved in a volatile solvent, which is immiscible with liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved/ dispersed in coating polymer solution with agitation, core: coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsules. The mixture then heated or

vacuum is applied to evaporate the solvent from the polymer. In the case where the core material is dissolved in coating polymer solution, matrix type microcapsules also called as Microspheres are formed.

METHADOLOGY

STEPS INVOLVED IN DEVELOPMENT OF SUSPENSION

Step 1: PREPARATION OF RESINATES

Selection of Resin

Resins can be selected on the basis of the nature of drug and requirement of formulation. Depending on the basis of acidic and basic nature of the drug, cation and anion exchange resins can be used. For basic drugs cation exchange resins are used and for acidic drugs, anion exchange resins are used.

Resin pretreatment

The pretreatment to the resin was given to get uniform size resin particles, to remove organic and colored impurities. The resin was activated for exchange by the alternate treatment to the NaOH and HCl.

The resin was treated with 5 to 10 bed volume of deionised water and the ultra fine particles, which were suspended, were removed to get uniform particle size. The resin was washed consecutively with methanol, benzene, and deionised water to remove organic and colored impurities. The resin was activated with alternate treatment with 1 N Hcl and 1 N NaOH in order to remove the resin derived products in solution. Finally the resin bed was treated with 1N Hcl for 4 hours & then rinsed with deionised water till free from excess of H^+ ions, which was determined by pH meter. The resin was then drained on a Buchner funnel using mild suction and then air-dried.
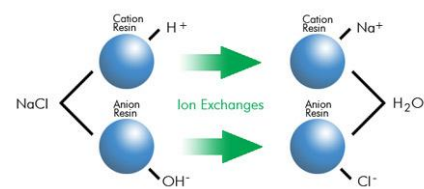
Pre formulation studies for Resin

i. Estimation of Moisture Content for Pretreated resin

One gram of accurately weighed air-dried pretreated resin was kept in an oven (previously heated at 1000 C) for 24 hours at 1000C and weighed. The difference in the weight of resin before and after drying gave the moisture content.

ii. Particle size determination of resin

Particle size of the resin was determined using optical microscope. The scale in the eyepiece micrometer was first calibrated for getting a factor. By multiplying the reading with this factor, we can directly get results in microns units. Particles were mounted on slide and placed on mechanical stage and the sizes of the particles were measured.

Preparation of Drug + Resin Complex (Resinates)

An accurately weighed amount of resin particles were suspended in mixture of methanol: deionised water (1:1) for 15 min. to allow uniform swelling of polymer, after which drug was added and slurry was stirred with the help of Magnetic stirrer for 1hr. to allow the maximum adsorption of drug on to the resin. Resinate thus formed was filtered and washed with solvent. It was then dried at 500C and the drug Content was determined spectrometrically at 278nm.

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Characterization for Drug + resin complex

i. Determination of drug content in the resinate:

Resinate so prepared by the batch process, were evaluated for the drug content.   100mg of resinate was stirred with 100ml of 0.1 M methanolic HCl till the entire drug was leached out. Then the Suspension was filtered and further dilutions were made. The drug content was noted spectrometrically at 278nm using 0.1 M methanolic HCl as blank.

ii. *In-Vitro* release profile of resinate

A dissolution study of dosage form is considered as one of the most important quality control tools while assessing efficacy of a product. In-vitro studies of drug release rate are useful in predicting the drug release pattern in vivo. However due to complexities involved in the mechanism of drug release in vivo it becomes difficult to correlate in-vivo release when tested in vitro.

Resinate prepared in 1:1 (drug: resin) ratio at pH 5.0 was subjected to study release characteristics using U.S.P. dissolution test apparatus in gastric simulated without enzyme fluid for first 2 hours followed by in pH 4 buffer for next 2 hours and pH 7.2 buffer for remaining 4 hours. 60mg of drug equivalent resinate was placed in basket surrounded by muslin cloth which retained the formulation. The dissolution medium was maintained at $37^0C \pm 1^0C$. The basket was rotated at 50 rpm, sample (1ml) was withdrawn after every 1 hr. (For total 8 hr.) and its absorbance was measured at 278 nm.

iii. Drug leaching study:

 Sustained release suspension was formulated by using optimized batch of microencapsulated resinate and it was studied for the leaching of drug in the surrounding medium of the developed suspension.

Step 2: MICROENCAPSULATION OF RESINATES USING ETHYLCELLULOSE

Preparation of micro capsulation by Solvent Evaporation techniques

Accurately weighed quantity of polymer i.e., ethyl cellulose was dissolved in 40ml of ethanol. Resinate was passed through the sieve # 100 so as to obtain the particle size that is easily dispersible. Weighed quantity of drug- resin complex was then dispersed in above polymer solution; it was stirred for 2 hrs at 400 rpm. The solvent ethanol is evaporated by continuous stirring on water bath. Stirring rate was gradually increased as the viscosity of the mixture was increased. The product was filtered and washed 3 times with cyclohexane and air-dried.

The microcapsules were separately prepared using Ethyl cellulose in different concentration, mainly 5, 10, 15, and 20% W/W of ethyl cellulose is used to prepare microencapsules of resinate following the same procedure.

Drug proportion was maintained constant so as to determine maximum polymer required to encapsulate drug, and to obtain desired drug release.

Pre formulation studies for microcapsules

i) Particle size determination
Size distribution plays a very important role in determining the release characteristics of the microcapsules. Various methods are used to determine particle size such as,

   i.   Optical microscopy,

   ii.   Sieving,

   iii. Particle volume measurements.

Optical microscopy method was used to determine particle size distribution. Microcapsules have the size range of 1-2000 μm. Particle size determination for about 50 microcapsules of various batches were carried out.

The scale in the eyepiece micrometer was first calibrated for getting a factor. By multiplying the reading with this factor, we can directly get results in microns units. The factor is

$$1 \text{ div} = 3.6619 \text{ μm}$$

Particles were mounted on slide and placed on mechanical stage and the sizes of the particles were measured.

Evaluation of Microcapsules

i) *In vitro* studies
In-vitro dissolution testing of oral dosage forms is an important tool, not only to assure product uniformity, but also to screen and optimize formulations during product development. Stressed conditions are encouraged in the latter case to detect possible critical formulation variables. The tests are performed by several types of apparatus, e.g., the Paddle, the Basket, etc.

Dissolution conditions are aimed at mimicking the physiological conditions of gastrointestinal tract considering pH, agitation, and temperature.

ii) Drug leaching study: Sustained release suspension was formulated by using optimized batch of microencapsulated resinate and it was studied for the leaching of drug in the surrounding medium of the developed suspension.

Step 3: DEVELOPMENT OF SUSPENSION

For the formulation of oral sustained release suspension optimized ratios of resinate and microencapsulated resinate were selected.

EVALUATION OF SUSPENSION

Sedimentation volume:

It is defined as the ratio of final volume of sediment to its initial volume

The measurement of sedimentation volume was done after storing each suspension for 24 hrs at room temperature, without disturbing it.

It is calculated using following formula,

$$Vs = H/Ho * 100,$$

Where,

H = Ultimate settled height, Ho = Original height of the suspension.

Determination of drug content

For the determination of drug content a suspension containing 100mg equivalent of the drug is filtered of and the drug content was determined as mentioned previously.

Drug leaching from suspension:

The most critical problems in the development of the pharmaceutical sustained release suspension is the leaching of the drug in surrounding medium. To determine the drug eluted in the vehicle 10ml of the suspension was filtered with the aid of whatman's filter paper and drug content was determined as mentioned previously.

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Resuspendability:

If a pharmaceutical suspension produce sediment on storage, it is essential that it should be radially dispersible on shaking so that uniformity of doses is assured. Each suspension was stored for 24 hrs without disturbing it. Then number of shakes or strokes required to resuspend the sediment were calculated by shaking it on the shaker.

In-vitro drug release profile of sustained release suspension

The drug release profile of the selected batches of suspensions containing resinate and microencapsulated resinate was carried out in buffer solution of pH 6.8 as dissolution media by using USP 23 dissolution apparatus.

Stability studies of developed sustained release suspension

The optimized batch of the sustained release suspension containing microencapsulated resinate subjected to stability testing for about 30 days. The temperatures were 37, 45^{0}C (incubator), and room temperature.

The optimized batch of sustained release suspension containing microencapsulated resinate is also subjected to the study of any change in the dissolution profile which are stored at different temperatures for one month. The dissolution studies are carried out as that of previously mentioned procedure for suspension.

CONCLUSION

The project was undertaken mainly considering the pediatric, geriatric and those patients, which are unable to take the solid dosage form. The rational behind the formulation development of the sustained release suspension is

- Improved patient compliance due to less frequent administration.
- Reduced in fluctuation in steady state level.
- To improve aesthetic value and palatability of the preparation by means of taste masking of bitter and unpleasant drugs.
- Reduction in side effects and improvement in bioavailability.
- Maximum utilization of drug resulting in reduction in total amount of dose administration.

Therefore in future change in type of resin or the type of drug leads to change in the different pharmaceutical characteristics of the present formulation hence, in future it is decided to work on development and evaluation of sustained release suspension with other types of drugs and resins and also it is decided to develop and evaluate a sustained release suspension containing microencapsulated drug-resin complex with more than one drug.

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